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## OPTIMAL STRATEGIES IN THE TREATMENT OF CANCERS IN THE LOTKA–VOLTERRA MATHEMATICAL MODEL OF COMPETITION

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The Lotka–Volterra competition model is applied to describe the interaction between the concentrations of healthy and cancer cell in diseases associated with blood cancer. The model is supplemented with a differential equation characterizing the change in the concentration of a chemotherapeutic drug. The equation contains a scalar bounded control that specifies the intensity of drug intake. We consider the problem of minimizing the weighted difference between the concentrations of cancer and healthy cells at the end time of the treatment period. The properties of an optimal control are established analytically with the use of the Pontryagin maximum principle. We describe situations in which the optimal control is a relay function and situations in which the control may contain a segment with a singular arc in addition to relay segments. The results obtained are confirmed by corresponding numerical calculations.

Keywords: Lotka–Volterra competition model, nonlinear control system, Pontryagin maximum principle, switching function, bang-bang control, singular arc.

### REFERENCES

1. Todorov Y., Fimmel E., Bratus A., Semenov Y., Nuernberg F. An optimal strategy for leukemia therapy: a multi-objective approach. *Russ. J. Numer. Anal. Math. Model.*, 2011, vol. 26, no. 6, pp. 589–604. doi: 10.1515/rjnamm.2011.035.
2. Bratus A.S., Fimmel E., Todorov Y., Semenov Y.S., Nürnberg F. On strategies on a mathematical model for leukemia therapy. *Nonlinear Analysis: Real World Appl.*, 2012, vol. 13, no. 3, pp. 1044–1059. doi: 10.1016/j.nonrwa.2011.02.027.
3. Bratus A.S., Goncharov A.S., Todorov I.T. Optimal control in a mathematical model for leukemia therapy with phase constraints. *Moscow Univ. Comput. Math. Cybern.*, 2012, vol. 36, no. 4, pp. 178–182. doi: 10.3103/S0278641912040024.
4. Bratus A., Todorov Y., Yegorov I., Yurchenko D. Solution of the feedback control problem in the mathematical model of leukaemia therapy. *J. Optim. Theory Appl.*, 2013, vol. 159, no. 3, pp. 590–605. doi: 10.1007/s10957-013-0324-6.
5. Fimmel E., Semenov Y., Bratus A. On optimal and suboptimal treatment strategies for a mathematical model of leukemia. *Math. Biosci. Eng.*, 2013, vol. 10, no. 1, pp. 151–165. doi: 10.3934/mbe.2013.10.151.
6. Egorov I.E. Assessing alternative control strategies for systems with asymptotically stable equilibrium positions. *Moscow Univ. Comput. Math. Cybern.*, 2013, vol. 37, no. 3, pp. 112–120. doi: 10.3103/S0278641913030059.
7. Solé R.V., Deisboeck T.S. An error catastrophe in cancer? *J. Theor. Biol.*, 2004, vol. 228, pp. 47–54. doi 10.1016/j.jtbi.2003.08.018.
8. Solé R.V., Garcia I.G., Costa J. Spatial dynamics in cancer. In: Deisboeck T.S., Kresh J.Y. (eds), *Complex Systems Science in Biomedicine*. Topics in Biomedical Engineering International Book Series. N Y: Springer, 2006, pp. 557–572. doi: 10.1007/978-0-387-33532-2\_24.
9. Kuchumov A.G. Mathematical modelling and biomechanical approach to describe the development, the diagnostics, and the treatment of oncological diseases. *Russian Journal of Biomechanics*, 2010, vol. 14, no. 4, pp. 42–69. (in Russian)
10. Khailov E.N., Klimenkova A.D., Korobeinikov A. Optimal control for anticancer therapy. In: Korobeinikov A., Caubergh M., Lázaro T., Sardanyés J. (eds), *Extended Abstracts Spring 2018*. Ser. Trends in Mathematics, vol. 11. Basel: Birkhäuser, 2019, pp. 35–43. doi: 10.1007/978-3-030-25261-8\_6.

11. Bratus' A.S., Novozhilov A.S., Platonov A.P. *Dinamicheskie sistemy i modeli biologii* [Dynamic systems and models in biology]. Moscow: Fizmatlit Publ., 2010, 400 p. ISBN: 978-5-9221-1192-8.
12. Tarasevich Yu.Yu. *Matematicheskoe i komp'yuternoe modelirovanie: Vvodnyi kurs* [Mathematical and computer modeling: Introductory course]. Moscow: Librokom Publ., 2013, 152 p. ISBN: 978-5-397-03828-7.
13. Hartman Ph. *Ordinary differential equations*. N Y: John Wiley & Sons, 1964, 612 p. Translated to Russian under the title *Obyknoennyye differentsial'nye uravneniya*. Moscow: Mir Publ., 1970, 720 p.
14. Lee E.B., Markus L. *Foundations of optimal control theory*. N.Y.; London; Sydney: John Wiley & Sons, Inc., 1967, 576 p. ISBN: 9780471522638. Translated to Russian under the title *Osnovy teorii optimal'nogo upravleniya*, Moscow: Nauka Publ., 1972, 576 p.
15. Vasil'ev F.P. *Metody optimizatsii* [Optimization methods]. Moscow: Factorial Press, 2002, 824 p. ISBN: 5-88688-056-9.
16. Schättler H., Ledzewicz U. *Geometric optimal control: theory, methods and examples*. N Y; Heidelberg; Dordrecht; London: Springer, 2012, 640 p. ISBN: 978-1-4614-3834-2.
17. Schättler H., Ledzewicz U. *Optimal control for mathematical models of cancer therapies: an applications of geometric methods*. N Y; Heidelberg; Dordrecht; London: Springer, 2015, 496 p. doi: 10.1007/978-1-4939-2972-6.
18. Zelikin M.I., Borisov V.F. *Theory of chattering control with applications to astronautics, robotics, economics, and engineering*. Boston: Birkhäuser, 1994, 244 p. doi: 10.1007/978-1-4612-2702-1.
19. Levin A.Yu. Non-oscillation of solutions of the equation  $x^n + p_1(t)x^{n-1} + \dots + p_n(t)x = 0$ . *Russian Math. Surveys*, 1969, vol. 24, no. 2, pp. 43–99. doi: 10.1070/RM1969v024n02ABEH001342.
20. Zelikin M.I., Zelikina L.F. The deviation of a functional from its optimal value under chattering decreases exponentially as the number of switchings grows. *Differ. Equ.*, 1999, vol. 35, no. 11, pp. 1489–1493.
21. Zhu J., Trélat E., Cerf M. Planar titling maneuver of a spacecraft: singular arcs in the minimum time problem and chattering. *Discrete Cont. Dyn.-B*, 2016, vol. 21, no. 4, pp. 1347–1388. doi: 10.3934/dcdsb.2016.21.1347.
22. Yegorov I., Mairet F., Gouzé J.-L. Optimal feedback strategies for bacterial growth with degradation, recycling, and effect of temperature. *Optim. Control Appl.*, 2018, vol. 39, no. 2, pp. 1084–1109. doi: 10.1002/oca.2398.
23. Grigorieva E., Khailov E. Chattering and its approximation in control of psoriasis treatment. *Discrete Contin. Dyn. Syst., Ser. B*, 2019, vol. 24, no. 5, pp. 2251–2280. doi: 10.3934/dcdsb.2019094.
24. Bonnans F., Martinon P., Giorgi D., Grélard V., Maindault S., Tissot O., Liu J. *BOCOP 2.0.5 – user guide*. 2017. Available at: URL: <http://bocop.org>.

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